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Highly Enantioselective Copper-Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2-Cyclohexenones

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General procedure for the kinetic resolution of **1a**, **1b**, **1d** and **3** on an analytical scale:

All resolution were performed on a 1 mmol scale with 1 mol% $Cu(OTf)_2$ and 2 mol% of the phosphoramidite ligand with *n*-dodecane as internal standard according to the general procedure (vide infra).

Typical experimental procedure for the resolution of racemic **1a** on an analytical scale; In flame dried glassware under an argon atmosphere 3.6 mg (0.01 mmol) $Cu(OTf)_2$ and 10.8 mg (0.02 mmol) (*S*,*R*,*R*)-**L1** were dissolved in 10 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to –40°C and 110 mg (1.0 mmol) racemic **1a** and 40 ìL *n*-dodecane (internal standard) were added. After stirring for 10 min 0.73 mL Et_2Zn (1.1 M

in toluene, 0.8 mmol) was added. Samples of 0.2 mL were taken after 2, 5, 10, 15, 20, 25, 30, 45 and 60 min. The samples were quenched in 1 mL Et_2O saturated with water and filtered over a small plug of silica. The silica plugs were thoroughly rinsed with the "wet" Et_2O. Both conversion and *ee* were determined by chiral GC. Chiraldex G-TA, 50 m × 0.25 mm, He-flow: 1.0 mL/min, 100°C isotherm. T_{ret} 13.4 min (*n*-dodecane), T_{ret} 21.6 min ((*S*)-**1a**), T_{ret} 22.7 min ((*R*)-**1a**).

Determination of conversion and *ee* for **1a**.

In all cases *ee* and conversion were determined by GC on a Chiraldex G-TA column (vide supra) except for the resolution performed with Me_2Zn because in this case the peaks of (*S*)-**1a** and addition product showed overlap. *Ee* and conversion were therefore measured on a Chiraldex A-TA column.

Determination of conversion and *ee* for **1b**.

Ee and conversion were determined by GC on a Hydrodex-B-3P column, 25 m × 0.25 mm, He-flow: 0.9 mL/min. Initial temp: 90°C, initial time: 10 min, rate: 5°C/min, final temp: 150°C. T_{ret} 17.5 min (*n*-dodecane), T_{ret} 21.9 min ((*S*)-**1b**), T_{ret} 22.1 min ((*R*)-**1b**).

Determination of conversion and *ee* for **1d**.

Ee and conversion were determined by GC on a CP-Chirasil-Dex CB column, 25 m × 0.25 mm, He-flow: 1.0 mL/min. Initial temp: 125°C, initial time: 20 min, rate: 10°C/min, final temp: 175°C. T_{ret} 6.0 min (*n*-dodecane), T_{ret} 10.9 min ((*S*)-**1d**), T_{ret} 11.4 min ((*R*)-**1d**).

Determination of conversion and *ee* for **3**.

Ee and conversion were determined by GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 mL/min, 100°C isothermic. T_{ret} 13.4 min (*n*-dodecane), T_{ret} 20.1 min ((*R*)-**3**), T_{ret} 20.8 min ((*S*)-**3**).

Procedure for the kinetic resolution of **1c**.

In flame dried glassware under an argon atmosphere 10.5 mg (0.03 mmol) $Cu(OTf)_2$ and 31.3 mg (0.06 mmol) (*S*,*R*,*R*)-**L1** were dissolved in 20 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to -35°C and 1.0 g (5.8 mmol) racemic **1c** and 0.40 mL *n*-hexadecane (internal standard) were added. After stirring for 10 min 2.85 mL Et_2Zn (1.1 M in toluene, 3.1 mmol) was added. After stirring overnight at –35°C a sample (0.2 mL) was taken. The sample was quenched in 1 mL Et_2O saturated with water and filtered over a small plug of silica. The silica plug was thoroughly rinsed with the

wet Et_2O. Analyses on a DB-1 (J&W) GC column showed that the conversion was 55%. The reaction mixture was quenched with 20 mL of 1N HCl (aq) and the aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvents yielded a mixture of **1c**, addition product and *n*-hexadecane which were seperated by column chromatography (SiO_2, hexanes-ether: 5-1) giving 378 mg (2.2 mmol, 38%) of (*R*)-(–)-**1c**. α_D^{20} = –37.9° (c = 1.97, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): ä 2.5-2.8 (m, 4H), 3.4, (m, 1H), 6.1-6.2 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.4 (m, 5H). ^{13}C-NMR (300MHz, $CDCl_3$): ä 33.64 (t), 40.91 (d), 44.81 (t), 126.64 (d), 126.94 (d), 128.72 (d), 129.73 (d), 143.13 (s), 149.47 (d), 199.15 (s). HPLC analysis (Chiralcel OJ, heptane-isopropanol: 95-5, flowrate 1.0 mL/min, $ë_{det}$ = 220 nm) showed *ee* = 89%.